	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	189	beta-catenin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:26			0
2	BRS	L2	7862	lef-1 or tcf-4 or apc or conductin or e-cadherin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:27			0
3	BRS	L3	85	1 same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:33			0
4	BRS	L5	0	(peptide or agent) same (inhibit or promomot or affect) same 4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:29			0
5	BRS	L4	27	3 same interaction	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:29			0
6	BRS	L6	0	1 same 2 same illness	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:35			0
7	BRS	L7	0	1 same illness	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:35			0
8	BRS	L8	17	1 same agent	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:39			0
9	BRS	L10	19	(his adj "470") or (arg adj "469") or (trp adj "383") or (arg adj "386") or (phe adj "253") or (arg adj "274") or (trp adj "338")	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:44			0
10	BRS	L11	0	9 same 10	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:46			0
11	BRS	L12	21	9 same (peptide or domain)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:44			0
12	BRS	L13	0	1 same 10	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:47			0
13	BRS	L9	58	1 same mutation	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/28 14:47			0

> d his

(FILE 'HOME' ENTERED AT 14:52:14 ON 28 JUL 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
14:53:00 ON 28 JUL 2002
L1 13144 S BETA-CATENIN
L2 55071 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L3 5750 S L1 (P) L2
L4 1449 S L3 (P) INTERACT?
L5 16 S L4 (P) (PEPTIDE OR AGENT) (P) (IINHIBIT? OR PROMOT? OR AFFEC
L6 40 S L4 (P) (PEPTIDE OR AGENT) (P) (INHIBIT? OR PROMOT? OR AFFECT
L7 11 DUPLICATE REMOVE L6 (29 DUPLICATES REMOVED)
L8 84 S (HIS 470) OR (ARG 469) OR (TRP 383) OR (ARG 386) OR (PHE 253)
L9 0 S L8 (P) L1
L10 3359 S L1 (P) MUTAT?
L11 123 S (HIS470) OR (ARG469) OR (TRP383) OR (ARG386) OR (PHE253) OR (
L12 0 S L1 (P) L11
L13 1859 S L10 (P) L2
L14 1449 S L3 (P) INTERACT?
L15 66 S L14 (P) (DISEASE OR ILLNESS)
L16 23 DUPLICATE REMOVE L15 (43 DUPLICATES REMOVED)
L17 17 S L1 (P) (ARMADILLO DOMAIN)
L18 5 S L17 (P) L2
L19 2 DUPLICATE REMOVE L18 (3 DUPLICATES REMOVED)
L20 5 S L4 (P) (N-TERMINAL) (P) (PAPTEIDE OR FRAGMENT)
L21 1 DUPLICATE REMOVE L20 (4 DUPLICATES REMOVED)

=> log y

```
FILE 'HOME' ENTERED AT 14:52:14 ON 28 JUL 2002

=> file medline caplus biosis embase scisearch agricola
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 14:53:00 ON 28 JUL 2002

FILE 'CAPLUS' ENTERED AT 14:53:00 ON 28 JUL 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 14:53:00 ON 28 JUL 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'EMBASE' ENTERED AT 14:53:00 ON 28 JUL 2002
COPYRIGHT (C) 2002 Elsevier Science B.V.  All rights reserved.

FILE 'SCISEARCH' ENTERED AT 14:53:00 ON 28 JUL 2002
COPYRIGHT (C) 2002 Institute for Scientific Information (ISI) (R)

FILE 'AGRICOLA' ENTERED AT 14:53:00 ON 28 JUL 2002

=> s beta-catenin
L1       13144 BETA-CATENIN

=> s lef-1 or tcf-4 or apc or conductin or e-cadherin
L2       55071 LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN

=> s l1 (p) l2
L3        5750 L1 (P) L2

=> s l3 (p) interact?
L4        1449 L3 (P) INTERACT?

=> s l4 (p) (peptide or agent) (p) (iinhibit? or promot? or affect?)
L5          16 L4 (P) (PEPTIDE OR AGENT) (P) (IINHIBIT? OR PROMOT? OR AFFECT?)


=> s l4 (p) (peptide or agent) (p) (inhibit? or promot? or affect?)
   4 FILES SEARCHED...
L6          40 L4 (P) (PEPTIDE OR AGENT) (P) (INHIBIT? OR PROMOT? OR AFFECT?)

=> duplicate remove l6
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L6
L7           11 DUPLICATE REMOVE L6 (29 DUPLICATES REMOVED)

=> d l7 1-11 ibib abs

L7   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        2002:554870  CAPLUS
TITLE:                   Regulation of S33/S37 phosphorylated .beta.-catenin in
                         normal and transformed cells
AUTHOR(S):               Sadot, Einat; Conacci-Sorrell, Maralice; Zhurinsky,
                         Jacob; Shnizer, Dalia; Lando, Zeev; Zharhary, Dorit;
                         Kam, Zvi; Ben-Ze'ev, Avri; Geiger, Benjamin
CORPORATE SOURCE:        Department of Molecular Cell Biology, Weizmann
                         Institute of Science, Rehovot, 76100, Israel
SOURCE:                  Journal of Cell Science (2002), 115(13), 2771-2780
                         CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER:               Company of Biologists Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   A novel phosphorylation-specific antibody (.alpha.p.  ***beta***  .-
       ***catenin***  ) was generated against a  ***peptide***  corresponding
     to amino acids 33-45 of human .  ***beta***  .-  ***catenin***  , which
```

contained phosphorylated serines at positions 33 and 37. This antibody is specific to phosphorylated . ***beta*** .- ***catenin*** and reacts neither with the non-phosphorylated protein nor with phosphorylated or non-phosphorylated plakoglobin. It weakly ***interacts*** with S33Y . ***beta*** .- ***catenin*** but not with the S37A mutant. P. ***beta*** .- ***catenin*** is hardly detectable in normal cultured cells and accumulates (up to 55% of total . ***beta*** .- ***catenin***) upon overexpression of the protein or after blocking its degrdn. by the proteasome. ***Inhibition*** of both GSK-3.beta. and the proteasome resulted in a rapid (t1/2=10 min) and reversible redn. in p. ***beta*** .- ***catenin*** levels, suggesting that the protein can undergo dephosphorylation in live cells, at a rate comparable to its phosphorylation by GSK-3.beta.. P. ***beta*** .- ***catenin*** ***interacts*** with ***LEF*** - ***1*** , but fails to form a ternary complex with DNA, suggesting that it is transcriptionally inactive. Immunofluorescence microscopy indicated that p. ***beta*** .- ***catenin*** accumulates in the nuclei of MDCK and BCAP cells when overexpressed and is transiently assocd. with adherens junctions shortly after their formation. P. ***beta*** .- ***catenin*** only weakly ***interacts*** with co-transfected N-cadherin, although it forms a complex with the ubiquitin ligase component .beta.-TrCP. SW480 colon cancer cells that express a truncated ***APC*** , at position 1338, contain high levels of p. ***beta*** .- ***catenin*** , whereas HT29 cells, expressing ***APC*** truncated at position 1555, accumulate non-phosphorylated . ***beta*** .- ***catenin*** , suggesting that the 1338-1555 amino acid region of ***APC*** is involved in the differential regulation of the dephosphorylation and degrdn. of p. ***beta*** .- ***catenin*** .

L7 ANSWER 2 OF 11 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002221111 MEDLINE
DOCUMENT NUMBER: 21957086 PubMed ID: 11960376
TITLE: UCS15A, a novel small molecule, SH3 domain-mediated protein-protein interaction blocking drug.
AUTHOR: Oneyama Chitose; Nakano Hirofumi; Sharma Sreenath V
CORPORATE SOURCE: Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd 3-6-6 Asahi-cho, Machida-shi, Tokyo 194, Japan.
SOURCE: ONCOGENE, (2002 Mar 27) 21 (13) 2037-50.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020418
Last Updated on STN: 20020511
Entered Medline: 20020510

AB Protein-protein ***interactions*** play critical regulatory roles in mediating signal transduction. Previous studies have identified an unconventional, small-molecule, Src signal transduction ***inhibitor*** , UCS15A. UCS15A differed from conventional Src- ***inhibitors*** in that it did not alter the levels or the tyrosine kinase activity of Src. Our studies suggested that UCS15A exerted its Src- ***inhibitory*** effects by a novel mechanism that involved the disruption of protein-protein ***interactions*** mediated by Src. In the present study we have examined the ability of UCS15A to disrupt the ***interaction*** of Src-SH3 with Sam68, both in vivo and in vitro. This ability of UCS15A was not restricted to Src-SH3 mediated protein-protein ***interactions*** , since the drug was capable of disrupting the in vivo ***interactions*** of Sam68 with other SH3 domain containing proteins such as Grb2 and PLCgamma. In addition, UCS15A was capable of disrupting other typical SH3-mediated protein-protein ***interactions*** such as Grb2-Sos1, cortactin-ZO1, as well as atypical SH3-mediated protein-protein ***interactions*** such as Grb2-Gab1. However, UCS15A was unable to disrupt the non-SH3-mediated protein-protein ***interactions*** of ***beta*** - ***catenin*** , with ***E*** - ***cadherin*** and alpha-catenin. In addition, UCS15A had no effect on the SH2-mediated ***interaction*** between Grb2 and activated Epidermal Growth Factor receptor. Thus, the ability of UCS15A, to disrupt protein-protein ***interactions*** appeared to be restricted to SH3-mediated protein-protein ***interactions*** . In this regard, UCS15A represents the first example of a non- ***peptide*** , small molecule ***agent***

capable of disrupting SH3-mediated protein-protein ***interactions*** . In vitro analyses suggested that UCS15A did not bind to the SH3 domain itself but rather may ***interact*** directly with the target proline-rich domains.

L7 ANSWER 3 OF 11 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002109278 MEDLINE
DOCUMENT NUMBER: 21819413 PubMed ID: 11818547
TITLE: Casein kinase I phosphorylates and destabilizes the beta-catenin degradation complex.
AUTHOR: Gao Zhong-Hua; Seeling Joni M; Hill Virginia; Yochum April; Virshup David M
CORPORATE SOURCE: Department of Oncological Sciences, Huntsman Cancer Institute, 2000 East North Campus Drive, University of Utah, Salt Lake City, UT 84112-5550, USA.
CONTRACT NUMBER: 2P30CA42014 (NCI)
R01CA71074 (NCI)
R01CA80809 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Feb 5) 99 (3) 1182-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020214
Last Updated on STN: 20020308
Entered Medline: 20020307

AB Wnt signaling plays a key role in cell proliferation and development. Recently, casein kinase I (CKI) and protein phosphatase 2A (PP2A) have emerged as positive and negative regulators of the Wnt pathway, respectively. However, it is not clear how these two enzymes with opposing functions regulate Wnt signaling. Here we show that both CKI delta and CKI epsilon ***interacted*** directly with Dvl-1, and that CKI phosphorylated multiple components of the Wnt-regulated ***beta*** - ***catenin*** degradation complex in vitro, including Dvl-1, adenomatous polyposis coli (***APC***), axin, and ***beta*** - ***catenin*** . Comparison of ***peptide*** maps from in vivo and in vitro phosphorylated ***beta*** - ***catenin*** and axin suggests that CKI phosphorylates these proteins in vivo as well. CKI abrogated ***beta*** - ***catenin*** degradation in Xenopus egg extracts. Notably, CKI decreased, whereas ***inhibition*** of CKI increased, the association of PP2A with the ***beta*** - ***catenin*** degradation complex in vitro. Additionally, ***inhibition*** of CKI in vivo stabilized the ***beta*** - ***catenin*** degradation complex, suggesting that CKI actively destabilizes the complex in vivo. The ability of CKI to induce secondary body axes in Xenopus embryos was reduced by the B56 regulatory subunit of PP2A, and kinase-dead CKI epsilon acted synergistically with B56 in ***inhibiting*** Wnt signaling. The data suggest that CKI phosphorylates and destabilizes the ***beta*** - ***catenin*** degradation complex, likely through the dissociation of PP2A, providing a mechanism by which CKI stabilizes ***beta*** - ***catenin*** and propagates the Wnt signal.

L7 ANSWER 4 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001640069 MEDLINE
DOCUMENT NUMBER: 21548408 PubMed ID: 11689703
TITLE: Cell density and phosphorylation control the subcellular localization of adenomatous polyposis coli protein.
AUTHOR: Zhang F; White R L; Neufeld K L
CORPORATE SOURCE: Department of Oncological Sciences, University of Utah, Salt Lake City, Utah 84112, USA.
CONTRACT NUMBER: 5PO1 CA73992-02 (NCI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2001 Dec) 21 (23) 8143-56. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107

Last Updated on STN: 20020123
Entered Medli[redacted] 20011205

AB Loss of functional adenomatous polyposis coli protein (***APC***) leads to uncontrolled proliferation of colonic epithelial cells, as evidenced by polyp formation, a prelude to carcinogenesis. As a tumor suppressor, ***APC*** targets the oncogene ***beta*** - ***catenin*** for proteasome-mediated cytoplasmic degradation. Recently, it was demonstrated that ***APC*** also ***interacts*** with nuclear ***beta*** - ***catenin*** , thereby reducing ***beta*** - ***catenin*** 's activity as a transcription cofactor and enhancing its nuclear export. The first objective of this study was to analyze how cellular context ***affected*** ***APC*** distribution. We determined that cell density but not cell cycle influenced ***APC*** 's subcellular distribution, with predominantly nuclear ***APC*** found in subconfluent MDCK and intestinal epithelial cells but both cytoplasmic and nuclear ***APC*** in superconfluent cells. Redistribution of ***APC*** protein did not depend on continual nuclear export. Focusing on the two defined nuclear localization signals in the C-terminal third of ***APC*** (NLS1(***APC***) and NLS2(***APC***)), we found that phosphorylation at the CK2 site increased and phosphorylation at the PKA site decreased NLS2(***APC***)-mediated nuclear translocation. Cell density-mediated redistribution of beta-galactosidase was achieved by fusion to NLS2(***APC***) but not to NLS1(***APC***). Both the CK2 and PKA sites were important for this density-mediated redistribution, and pharmacological ***agents*** that target CK2 and PKA instigated relocalization of endogenous ***APC*** . Our data provide evidence that physiological signals such as cell density regulate ***APC*** 's nuclear distribution, with phosphorylation sites near NLS2(***APC***) being critical for this regulation.

L7 ANSWER 5 OF 11 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001043101 MEDLINE
DOCUMENT NUMBER: 20404931 PubMed ID: 10949998
TITLE: Up-regulation of E-cadherin and I-catenin in human hepatocellular carcinoma cell lines by sodium butyrate and interferon-alpha.
AUTHOR: Masuda T; Saito H; Kaneko F; Atsukawa K; Morita M; Inagaki H; Kumagai N; Tsuchimoto K; Ishii A H
CORPORATE SOURCE: Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan.
SOURCE: IN VITRO CELLULAR AND DEVELOPMENTAL BIOLOGY. ANIMAL, (2000 Jun) 36 (6) 387-94.
Journal code: 9418515. ISSN: 1071-2690.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207

AB Human ***E*** - ***cadherin*** is a homophilic cell adhesion molecule and its expression is well preserved in normal human hepatocytes; a decrease in its expression has been observed in poorly differentiated hepatocellular carcinoma cells. We examined the alteration of ***E*** - ***cadherin*** and catenin expressions caused by differentiation inducers in human hepatocellular carcinoma cells. Hepatocellular carcinoma cell lines, HCC-T and HCC-M, were cultured with all-trans retinoic acid (ATRA), dexamethasone (DEX), sodium butyrate, and interferon-alpha. ***E*** - ***cadherin*** expression was only up-regulated by butyrate and interferon-alpha (IFN-alpha) in both cell lines, studied by means of fluorescence immunostaining and flow cytometry. The localization of ***E*** - ***cadherin*** staining was shown at their cell membrane. According to the increase in ***E*** - ***cadherin*** expression, ***beta*** - ***catenin*** expression appeared at the cell membrane of both cell lines when treated with butyrate and IFN-alpha. Such an appearance was not observed when cells were treated with ATRA and DEX. Western blotting showed that alpha- and y-catenin expression was not changed, while only the expression of ***beta*** - ***catenin*** increased. ***Beta*** - ***catenin*** oncogenic activation as a result of amino acid substitutions or interstitial deletions within or including parts of exon 3, which has been demonstrated recently, was not

detected in these cell lines by direct deoxyribonucleic acid sequencing. These results suggest that th[redacted]xpression and ***interaction[redacted] between ***E*** - ***cadherin*** and wild-type ***beta*** - ***catenin*** are potentially modulated by butyrate and IFN-alpha, and that these two ***agents*** are potent ***inhibitors*** of hepatocellular carcinoma cell invasion and metastasis.

L7 ANSWER 6 OF 11 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000102527 MEDLINE
DOCUMENT NUMBER: 20102527 PubMed ID: 10638989
TITLE: Butyrate regulates E-cadherin transcription, isoform expression and intracellular position in colon cancer cells.
AUTHOR: Barshishat M; Polak-Charcon S; Schwartz B
CORPORATE SOURCE: Institute of Biochemistry, Food Science and Nutrition, Faculty of Agricultural, Food and Environmental Quality Sciences, The Hebrew University of Jerusalem, Rehovot, Israel.
SOURCE: BRITISH JOURNAL OF CANCER, (2000 Jan) 82 (1) 195-203. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000131

AB Cell-to-cell adhesion, an important event in differentiation, is impaired during advanced stages of tumorigenesis. In this study, we examined the possible regulation of cell-adhesion proteins by the differentiation ***agent*** butyrate in LS174T and HM7 cells, two types of human colon cancer cells that differ in their ability to produce mucin and colonize the liver of experimental animals. The more aggressive, high-mucin-producing cell line (HM7), a clone selected from LS174T cells, showed a scattered and undifferentiated ultramorphological appearance and low basal alkaline phosphatase activity; the proteins ***beta*** - ***catenin*** and ***E*** - ***cadherin*** , as detected by immunostaining, were expressed in the cells' nuclei. All of these properties were significantly less pronounced in the less aggressive, low-mucin-producing LS174T cells. In both cell lines, butyrate treatment enhanced cell-to-cell ***interaction*** , alkaline phosphate activity, translocation of ***beta*** - ***catenin*** and ***E*** - ***cadherin*** from the nuclei to the membrane junctions, and transcription and translation of the 120-kDa ***E*** - ***cadherin*** isoform, but not of its 100-kDa isoform. Analysis of possible mechanisms of ***E*** - ***cadherin*** up-regulation revealed that butyrate induces the release of nuclear proteins from the ***E*** - ***cadherin*** ***promoter*** sequence, reducing transcription repression. We suggest that butyrate activates ***E*** - ***cadherin*** transcription through translocation of nuclear transcription factors bearing specific repressor activity. We surmise that abrogation of nuclear 100-kDa ***E*** - ***cadherin*** and ***beta*** - ***catenin*** expression following butyrate treatment is related to the control of ***E*** - ***cadherin*** gene transcription.

L7 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:549289 CAPLUS
DOCUMENT NUMBER: 131:194280
TITLE: Agents for treating cancer and other human illnesses based on .beta.-catenin
INVENTOR(S): Birchmeier, Walter; Von Kries, Jens-Peter
PATENT ASSIGNEE(S): Max-Delbrueck-Centrum fuer Molekulare Medizin, Germany
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 9942481	A2	19990[redacted]	WO 1999-DE554	19990222	
WO 9942481	A3	20000210			

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

DE 19909251	A1	19990826	DE 1999-19909251	19990222
EP 1054899	A2	20001129	EP 1999-913097	19990222
JP 2002505255	T2	20020219	JP 2000-532433	19990222

PRIORITY APPLN. INFO.: DE 1998-19807390 A 19980221
WO 1999-DE554 W 19990222

AB C. ***beta*** .- ***catenin*** is a central mol. of the Wnt signal path. Increasing . ***beta*** .- ***catenin*** in the cell leads to its translocation into the cell nucleus and to its ***interaction*** with transcription factors of the ***LEF*** - ***1*** /TCF family. This can lead to colonic cancers and melanomas (oncogenic signal path). However, . ***beta*** .- ***catenin*** also ***interacts*** with the tumor-suppressor genes ***APC*** , ***conductin*** , and ***E*** - ***cadherin*** , which have a contrary effect on the cell (antioncogenic effect). ***Peptides*** derived from ***LEF*** - ***1*** -/ ***TCF*** - ***4*** transcription factors and analogous mols. can be used in the treatment of tumors, esp. colonic cancers and melanomas. These ***peptides*** and analogous mols. influence the ***interaction*** between . ***beta*** .- ***catenin*** and ***LEF*** - ***1*** /TCF. The ***peptides*** comprise parts of the ***LEF*** - ***1*** / ***TCF*** - ***4*** transcription factors and variants and mutations thereof, preferably the 10-40 N-terminal amino acids of ***LEF*** - ***1*** or ***TCF*** - ***4*** , as well as ***peptides*** derived from the armadillo region of . ***beta*** .- ***catenin*** which were identified as ***interaction*** domains with ***LEF*** - ***1*** /TCF, ***APC*** , ***conductin*** , and ***E*** - ***cadherin*** . The ***peptides*** constituting ***interaction*** domains with ***APC*** or ***conductin*** can increase the concn. of . ***beta*** .- ***catenin*** in the cell. These last mols. can be used to influence the formation of tissues and organs, e.g. to ***promote*** hair growth.

L7 ANSWER 8 OF 11 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999452924 MEDLINE
DOCUMENT NUMBER: 99452924 PubMed ID: 10521419
TITLE: Suppression of glycogen synthase kinase activity is not sufficient for leukemia enhancer factor-1 activation.
AUTHOR: Yuan H; Mao J; Li L; Wu D
CORPORATE SOURCE: Department of Pharmacology, University of Rochester, New York 14642, USA.
CONTRACT NUMBER: GM53162 (NIGMS)
GM54167 (NIGMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Oct 22) 274 (43) 30419-23.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991123

AB Glycogen synthase kinase-3 (GSK) can be regulated by different signaling pathways including those mediated by protein kinase Akt and Wnt proteins. Wnt proteins are believed to activate a transcription factor leukemia enhancer factor-1 (***LEF*** - ***1***) by ***inhibiting*** GSK, and Akt was shown to phosphorylate GSK and ***inhibit*** its kinase activity. We investigated the effect of an activated Akt on the accumulation of cytosolic ***beta*** - ***catenin*** and ***LEF*** - ***1*** -dependent transcription. Although the activated Akt, mAkt, clearly ***inhibited*** the kinase activity of GSK, mAkt alone did not induce accumulation of cytosolic ***beta*** - ***catenin*** or activate ***LEF*** - ***1*** -dependent transcription. On the contrary, coexpressed Wnt-1 and Frat activated ***LEF*** - ***1*** but did not show significant ***inhibition*** of GSK-mediated

phosphorylation of a ***peptide*** substrate. However, mAkt could act synergistically with Wnt-1 or Frat to activate ***LEF*** - ***1*** . In addition, the ***interaction*** of GSK for Axin appeared to decrease in the presence of mAkt, whereas the ***interaction*** for Frat remained unchanged. Consistently, a GSK mutant with substitution of a Phe residue for residue Tyr-216, which showed one-fifth of kinase activity of the wild-type GSK, exhibited a reduced association for Axin than the wild-type GSK. These results suggest that ***inhibition*** of GSK kinase activity is not sufficient for activation of ***LEF*** - ***1*** but may facilitate the activation by reducing the ***interaction*** of GSK for Axin. The additional mechanism for ***LEF*** - ***1*** activation may require dissociation of GSK from Axin as Frat facilitates the dissociation of GSK from Axin.

L7 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:578401 CAPLUS
DOCUMENT NUMBER: 129:328962
TITLE: Studies on colon tumorigenesis and therapy using Apc knockout mice
AUTHOR(S): Taketo, Makoto M.
CORPORATE SOURCE: Laboratory of Biomedical Genetics, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan
SOURCE: Yakubutsu Dotai (1998), 13(3), 273-279
CODEN: YADOEL; ISSN: 0916-1139
PUBLISHER: Nippon Yakubutsu Dotai Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 44 refs., discussing the mol. genetic studies of familial adenomatous polyposis (FAP) kindreds which led to the discovery of the ***APC*** (adenomatous polyposis coli) gene on human chromosome 5q21. Mutations in ***APC*** appear to be responsible for not only FAP but also many sporadic cancers of the colorectal axis, stomach, and esophagus. The ***APC*** protein contains regions that may form an .alpha.-helical coiled-coil structure, and a sub-domain of the first 55 aa form a stable, parallel helical dimer. Antibody studies showed that the wild-type, but not mutant, ***APC*** protein is assocd. with the microtubule cytoskeleton. The predicted structure of ***APC*** , its localization, and its ***interaction*** with . ***beta*** .- ***catenin*** suggested its involvement in cell adhesion. In fact, recent studies demonstrated that ***APC*** is localized to plasma membrane sites involved in active cell migration. At the same time, . ***beta*** .- ***catenin*** ***interacts*** with hTcf-4 and Lef transcription factors, hTct-4 transactivates transcription only when assocd. with . ***beta*** .- ***catenin*** . We recently constructed a gene knockout mouse strain in which the mouse homolog of the human ***APC*** was inactivated by homologous recombination. Using this mouse strain, we elucidated the mechanism how the polyp adenomas are formed in both morphol. and genetic aspects. At the same time, we investigated the effects of carcinogens and anticancer ***agents*** on the polypsis. Accumulating evidence indicates that nonsteroidal antiinflammatory drugs (NSAIDs) reduce the incidence of colorectal cancers in human and exptl. animals, and reduce the polyp no. and size in FAP patients. Recently, evidence has been presented that COX-2 is induced in human colorectal cancers, and in the polyps of mouse FAP models. Accordingly, we inactivated the COX-2 gene in our FAP model mice, and demonstrated that both the no. and size of polyps are reduced dramatically. In addn., a COX-2 selective ***inhibitor*** caused similar results to COX-2 gene knockout mutations. These genetic and pharmacol. data open the possibility of effectively treating human FAP and various cancers with COX-2 selective ***inhibitors*** , a new class of NSAIDs.

L7 ANSWER 10 OF 11 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998440064 MEDLINE
DOCUMENT NUMBER: 98440064 PubMed ID: 9769128
TITLE: TPA-induced cohort migration of well-differentiated human rectal adenocarcinoma cells: cells move in a RGD-dependent manner on fibronectin produced by cells, and phosphorylation of E-cadherin/catenin complex is induced independently of cell-extracellular matrix interactions.
AUTHOR: Nabeshima K; Inoue T; Shimao Y; Kataoka H; Koono M
CORPORATE SOURCE: Department of Pathology, Miyazaki Medical College,

Kiyotake, Japan
SOURCE: VIRCHOWS ARCHI (1998 Sep) 433 (3) 243-53.
Journal code: 9423843. ISSN: 0945-6317.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981029
Last Updated on STN: 19981029
Entered Medline: 19981022

AB We have already presented a two-dimensional cell motility assay using a highly metastatic variant (L-10) of human rectal adenocarcinoma cell line RCM-1 as a motility model of tumour cells of epithelial origin. In this model, L-10 cells showed locomotion as a coherent sheet when stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA), and we called this type of movement "cohort migration". Electron and immunoelectron microscopic study of the migrating cell sheets demonstrated localized release from cell-cell adhesion only at the lower portion of the cells with loss of ***E*** - ***cadherin*** immunoreactivity, and this change was associated with increased tyrosine phosphorylation of the ***E*** - ***cadherin*** -catenin complex, including ***beta*** - ***catenin*** . Cell-extracellular matrix (ECM) ***interactions*** involved in this TPA-induced cohort migration and their effect on tyrosine phosphorylation of the ***E*** - ***cadherin*** -catenin complex have now been investigated. L-10 cell cohort migration was almost completely ***inhibited*** by addition of Arg-Gly-Asp (RGD) ***peptide*** into the medium, and thus RGD dependent. Cohort migration was stimulated on type I and IV collagens, fibronectin (FN)- and laminin-coated substratum, but was ***inhibited*** by RGD only on FN-coated surface. By using immunofluorescent techniques, FN was demonstrated preferentially around migrating cells, and a protein synthesis ***inhibitor*** , cycloheximide, ***inhibited*** the migration by about 75%. FN produced by L-10 cells were found to be mostly EDA+ FN when analysed by RT-PCR. Moreover, anti-FN antibody, but not anti-vitronectin antibody, ***inhibited*** the TPA-induced cohort migration almost completely. Thus, it was likely that L-10 cells produced FN themselves and moved on the FN substrate in an RGD-dependent manner. However, stimulation of migration by type I collagen coating and ***inhibition*** by RGD treatment did not ***affect*** the tyrosine phosphorylation of the ***E*** - ***cadherin*** -catenin complex induced by TPA, indicating that cell-cell ***interactions*** were adjusted to suit cell migration, irrespective of the condition of cell-ECM adhesion, during TPA-induced cohort migration.

L7 ANSWER 11 OF 11 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998162711 MEDLINE
DOCUMENT NUMBER: 98162711 PubMed ID: 9501980
TITLE: Nuclear localization signal-independent and importin/karyopherin-independent nuclear import of beta-catenin.
AUTHOR: Fagotto F; Gluck U; Gumbiner B M
CORPORATE SOURCE: Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, New York 10021, USA.
CONTRACT NUMBER: GM37432 (NIGMS)
P30-CA-08748 (NCI)
SOURCE: CURRENT BIOLOGY, (1998 Feb 12) 8 (4) 181-90.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980513

AB BACKGROUND: Control of the nuclear localization of specific proteins is an important mechanism for regulating many signal transduction pathways. Upon activation of the Wnt signaling pathway, ***beta*** - ***catenin*** localizes into the nucleus and ***interacts*** with TCF/ ***LEF*** - ***1*** (T-cell factor/lymphocyte enhancer factor-1) transcription factors, triggering activation of downstream genes. The role of regulated

nuclear localization in ***beta*** - ***catenin*** signaling is still unclear. ***Beta*** [redacted] ***catenin*** has no nuclea[redacted] localization sequence (NLS). Although it has been reported that ***beta*** - ***catenin*** can piggyback into the nucleus by binding to TCF/ ***LEF*** - ***1*** , there is evidence that its import is independent of TCF/ ***LEF*** - ***1*** in vivo. Therefore, the mechanism for ***beta*** - ***catenin*** nuclear localization remains to be established. RESULTS: We have analyzed ***beta*** - ***catenin*** nuclear import in an in vitro assay using permeabilized cells. ***Beta*** - ***catenin*** docks specifically onto the nuclear envelope in the absence of other cytosolic factors. Docking is not ***inhibited*** by an NLS ***peptide*** and does not require importins/karyopherins, the receptors for classical NLS substrates. Rather, docking is specifically competed by importin-beta/beta-karyopherin, indicating that ***beta*** - ***catenin*** and importin-beta/beta-karyopherin both ***interact*** with common nuclear pore components. Nuclear translocation of ***beta*** - ***catenin*** is energy dependent and is ***inhibited*** by nonhydrolyzable GTP analogs and by a dominant-negative mutant form of the Ran GTPase. Cytosol preparations contain ***inhibitory*** activities for ***beta*** - ***catenin*** import that are distinct from the competition by importin-beta/beta-karyopherin and may be involved in the physiological regulation of the pathway. CONCLUSIONS: ***Beta*** - ***catenin*** is imported into the nucleus by binding directly to the nuclear pore machinery, similar to importin-beta/beta-karyopherin or other importin-beta-like import factors, such as transportin. These findings provide an explanation for how ***beta*** - ***catenin*** localizes to the nucleus without an NLS and independently of its ***interaction*** with TCF/ ***LEF*** - ***1*** . This is a new and unusual mechanism for the nuclear import of a signal transduction protein. The lack of ***beta*** - ***catenin*** import activity in the presence of normal cytosol suggests that its import may be regulated by upstream events in the Wnt signaling pathway.

```
=> d his

     (FILE 'HOME' ENTERED AT 14:52:14 ON 28 JUL 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     14:53:00 ON 28 JUL 2002
L1         13144 S BETA-CATENIN
L2         55071 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L3          5750 S L1 (P) L2
L4          1449 S L3 (P) INTERACT?
L5            16 S L4 (P) (PEPTIDE OR AGENT) (P) (IINHIBIT? OR PROMOT? OR AFFEC
L6            40 S L4 (P) (PEPTIDE OR AGENT) (P) (INHIBIT? OR PROMOT? OR AFFECT
L7            11 DUPLICATE REMOVE L6 (29 DUPLICATES REMOVED)

=> s (his 470) or (arg 469) or (trp 383) or (arg 386) or (phe 253) or (arg 274) or (trp 338)
L8            84 (HIS 470) OR (ARG 469) OR (TRP 383) OR (ARG 386) OR (PHE 253)
                 OR (ARG 274) OR (TRP 338)

=> s l8 (p) l1
L9             0 L8 (P) L1

=> s l1 (p) mutat?
L10         3359 L1 (P) MUTAT?

=> s (his470) or (arg469) or (trp383) or (arg386) or (phe253) or (arg274) or (trp338)
L11          123 (HIS470) OR (ARG469) OR (TRP383) OR (ARG386) OR (PHE253) OR
                 (ARG274) OR (TRP338)

=> s l1 (p) l11
L12            0 L1 (P) L11

=> s l10 (p) L2
L13         1859 L10 (P) L2

=> s l3 (p) interact?
L14         1449 L3 (P) INTERACT?
```

```
=> s l14 (p) (disease or illness)
L15         66 L14 (P) (DISEASE OR ILLNESS)

=> duplicate remove l15
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L15
L16          23 DUPLICATE REMOVE L15 (43 DUPLICATES REMOVED)

=> d l16 1-23 ibib abs

L16  ANSWER 1 OF 23  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:661652  CAPLUS
DOCUMENT NUMBER:          135:207457
TITLE:                    Modulation of pleiotrophin signaling by receptor-type
                          protein tyrosine phosphatase .beta./.zeta. and
                          therapeutic use
INVENTOR(S):              Deuel, Thomas
PATENT ASSIGNEE(S):       Barnes-Jewish Hospital, USA
SOURCE:                   PCT Int. Appl., 31 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2001064944      A1   20010907       WO 2001-US6476   20010228
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2000-185653P  P  20000229
AB   The mechanism by which pleiotrophin binds to the protein tyrosine
     phosphatase .zeta./receptor-like protein tyrosine phosphatase .beta. (RPTP
     .beta./.zeta.) is disclosed along with methods of modulating both
     pleiotrophin expression and signaling to treat, prevent and inhibit
     abnormal cell growth states.  Applicants have shown that RPTP
     .beta./.zeta. is the receptor for pleiotrophin.  Binding of RPTP
     .beta./.zeta. and pleiotrophin inhibits RPTP .beta./.zeta. enzymic
     activity and results in higher levels of tyrosine phosphorylation of .
       ***beta***  .-  ***catenin***  .  Further, binding of RPTP .beta./.zeta.
     and pleiotrophin also reduces the levels of .  ***beta***  .-
       ***catenin***  ***interaction***  with  ***E***  -  ***cadherin***
     and thus affects the potential for cells to adhere with each other.  The
     elucidation of this relationship between RPTP .beta./.zeta. and
     pleiotrophin can be used to define compds. useful in therapy and treating
       ***disease***  .  Specifically provided are methods of inhibiting tumor
     growth, promotion, metastasis, invasiveness and angiogenesis as well as
     methods of preventing or inhibiting cell adhesion.
REFERENCE COUNT:          3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16  ANSWER 2 OF 23     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2001685062     MEDLINE
DOCUMENT NUMBER:    21588223   PubMed ID: 11585828
TITLE:              ARM domain-dependent nuclear import of adenomatous
                    polyposis coli protein is stimulated by the B56 alpha
                    subunit of protein phosphatase 2A.
AUTHOR:             Galea M A; Eleftheriou A; Henderson B R
CORPORATE SOURCE:   Westmead Institute for Cancer Research, University of
                    Sydney, Westmead Millennium Institute at Westmead Hospital,
                    New South Wales 2145, Australia.
SOURCE:             JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Dec 7) 276 (49)
                    45833-9.
                    Journal code: 2985121R. ISSN: 0021-9258.
```

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Arti[redacted]; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011204
Last Updated on STN: 20020125
Entered Medline: 20020110

AB Inactivating mutations in the adenomatous polyposis coli (***APC***) gene correlate with progression of colon cancer and familial adenomatous polyposis. The ***APC*** tumor suppressor contributes to chromosome segregation and turnover of the oncogenic transcriptional activator ***beta*** - ***catenin*** , and these activities are impaired by truncating cancer mutations. ***APC*** was recently identified as a shuttling protein whose subcellular distribution is regulated by two nuclear localization signals (NLSs) and multiple nuclear export signals (NESs). Here, we show that mutant ***disease*** -linked truncated forms of ***APC*** , most of which lack the two central NLSs and certain NES sequences, retain nuclear-cytoplasmic shuttling activity. Nuclear export of truncated ***APC*** is mediated by a dominant N-terminal NES. Nuclear import of NLS-deficient ***APC*** mutants is facilitated by the N-terminal ARM domain. Furthermore, co-expression of the ARM-binding protein, B56 alpha, increased the nuclear localization of mutant and wild-type ***APC*** . The minimal B56 alpha-responsive sequence mapped to ***APC*** amino acids 302-625. B56 alpha is a regulatory subunit of protein phosphatase 2A; however, its ability to shift ***APC*** to the nucleus was independent of phosphatase activity. We conclude that ***APC*** nuclear import is regulated by the ARM domain through its ***interaction*** with B56 alpha and postulate that ***APC*** /B56 alpha complexes target the dephosphorylation of specific proteins within the nucleus.

L16 ANSWER 3 OF 23 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001567875 MEDLINE
DOCUMENT NUMBER: 21486490 PubMed ID: 11504726
TITLE: Presenilin 1 regulates beta-catenin-mediated transcription in a glycogen synthase kinase-3-independent fashion.
AUTHOR: Palacino J J; Murphy M P; Murayama O; Iwasaki K; Fujiwara M; Takashima A; Golde T E; Wolozin B
CORPORATE SOURCE: Department of Pharmacology and Neuroscience Program, Loyola University Medical Center, Maywood, Illinois 60153, USA.
CONTRACT NUMBER: 1F31MH12479 (NIMH)
AG17485 (NIA)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Oct 19) 276 (42) 38563-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011025
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Presenilin 1 (PS1) is linked with Alzheimer's ***disease*** but exhibits functional roles regulating growth and development. For instance, PS1 binds to ***beta*** - ***catenin*** and modulates ***beta*** - ***catenin*** signaling. In the current study, we observed that knockout of PS1 inhibited ***beta*** - ***catenin*** -mediated transcription by 35%, as shown by a luciferase reporter driven by the hTcf-4 promoter. Overexpressing wild-type PS1 increased ***beta*** - ***catenin*** -mediated transcription by 37.5%, and overexpressing PS1 with mutations associated with Alzheimer's ***disease*** decreased ***beta*** - ***catenin*** -mediated transcription by 66%. To examine whether regulation of ***beta*** - ***catenin*** by PS1 requires phosphorylation by glycogen synthase kinase 3beta (GSK 3beta), we examined whether inhibiting GSK 3beta activity overcomes the inhibition of ***beta*** - ***catenin*** transcription induced by mutant PS1 constructs. Cells expressing wild-type or mutant PS1 were treated with LiCl, which inhibits GSK 3beta, or transfected with ***beta*** - ***catenin*** constructs that lack the GSK 3beta phosphorylation sites. Neither treatment overcame PS1-mediated inhibition of ***beta*** -

catenin signaling, suggesting that regulation of ***beta*** - ***catenin*** by PS1 was affected by the activity of GSK3beta. To investigate how PS1 might regulate ***beta*** - ***catenin*** signaling, we determined whether PS1 ***interacts*** with other elements of the ***beta*** - ***catenin*** signaling cascade, such as the ***Tcf*** - ***4*** transcription factor. Coimmunoprecipitation studies showed binding of PS1 and hTcf-4, and examining nuclear isolates indicated that nuclear hTcf-4 was decreased in cells expressing mutant PS1. These data show that PS1 ***interacts*** with multiple components of the ***beta*** - ***catenin*** signaling cascade and suggest that PS1 regulates ***beta*** - ***catenin*** in a manner independent of GSK 3beta activity.

L16 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:519882 BIOSIS
DOCUMENT NUMBER: PREV200100519882
TITLE: Delta (delta) catenin in neuronal adherens junctions: Implications for adult brain function.
AUTHOR(S): Israely, I. (1); Kosik, K.; Liu, X. (1)
CORPORATE SOURCE: (1) Mol. and Med. Pharmacology, UCLA School of Medicine, Los Angeles, CA USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 947. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Understanding how the precise pattern of neural circuitry is specified at the molecular level is one of the fundamental issues underlying how the brain works. Adhesion molecules, such as cadherins, are good candidates for regulating synaptic specificity. delta-catenin, a member of the p120-catenin subfamily of Armadillo proteins, is a neuron specific adherens junction molecule that ***interacts*** with both ***E*** - ***cadherin*** and ***beta*** - ***catenin*** . In humans, hemizygous loss of delta-catenin correlates with the severity of mental retardation in Cri-du-Chat syndrome. Also, delta-catenin ***interacts*** with Presenilin 1, the protein most often mutated in Familial Alzheimer's ***Disease*** (F-AD). We generated mice with a targeted deletion of delta-catenin and confirmed that homozygous (d-cat-/-) mice lack delta-catenin and are viable, although survival is lower than that of WT isogenic littermates. To determine the role of delta-catenin in the establishment and strengthening of neuronal adherens junctions, we are comparing the architecture of neurons from d-cat-/- and WT mice. Additionally, to understand the importance of this protein for activity dependent synaptic changes, we are in the process of characterizing hippocampal synaptic physiology of d-cat-/- mice. To unravel the function of neuronal adhesive junctions in cognitive processes, such as learning and memory, we are evaluating spatial learning, place and social recognition, pavlovian fear conditioning and motor coordination in d-cat-/- mice. The results of these studies may have implications for neurodegenerative disorders such as AD.

L16 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:504036 BIOSIS
DOCUMENT NUMBER: PREV200100504036
TITLE: Presenilin-1 binds to cytoplasmic juxtamembrane region of E-cadherin and regulates stability and function of the cadherin adhesion complex.
AUTHOR(S): Marambaud, P. (1); Baki, L. (1); Efthimiopoulos, S. (1); Georgakopoulos, A. (1); Wen, P. (1); Shioi, J. (1); Robakis, N. K. (1)
CORPORATE SOURCE: (1) Psychiatry and Fishberg Research Center for Neurobiology, Mount Sinai School of Medicine, New York, NY USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 629. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001

ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Most cases of early onset familial Alzheimer's ***disease*** (FAD) are due to mutations in the presenilin-1 (PS1) gene. In epithelial cells, PS1 localizes at the plasma membrane of cell-cell contacts and ***interacts*** with the cadherin adhesion complex (Georgakopoulos et al., Mol Cell 1999, 4(6):893-902). We used ***E*** - ***cadherin*** deletion mutants which lack the ***beta*** - ***catenin*** and Y-catenin binding sequence to show that the PS1/ ***E*** - ***cadherin*** ***interaction*** is independent of the catenin binding. We found that PS1 binds to the membrane-proximal cytoplasmic sequence 604-615 of ***E*** - ***cadherin*** , a sequence also required for ***E*** - ***cadherin*** /p120 ***interaction*** . p120 is a cytosolic protein known to regulate cadherin-mediated cell-cell adhesion. Thus, PS1 and p120 mutually compete for ***E*** - ***cadherin*** binding. Furthermore, using wild type and PS1 deficient cells, we found that PS1 stabilizes the ***interaction*** between ***E*** - ***cadherin*** and ***beta*** - ***catenin*** or Y-catenin and increases the cytoskeletal association of the cadherin adhesion complex. As a consequence, PS1 increases calcium-dependent cell-cell aggregation whereas the PS1 FAD mutant DELTAE9 failed to stabilize the cadherin adhesion complex and to promote cell-cell adhesion. By stabilizing the cadherin/catenin complex, PS1 may regulate the Wnt pathway. Therefore, PS1 is a component and a regulator of the ***E*** - ***cadherin*** /catenin complex and FAD mutations may interfere with the cadherin-mediated adhesion in many tissues including the synapse and brain endothelium.

L16 ANSWER 6 OF 23 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002169871 MEDLINE
DOCUMENT NUMBER: 21901227 PubMed ID: 11903580
TITLE: Adenomatous polyposis coli (APC), beta-catenin, and cadherin are expressed in human bone and cartilage.
AUTHOR: Monaghan H; Bubb V J; Sirimujalin R; Millward-Sadler S J; Salter D M
CORPORATE SOURCE: Department of Pathology, Edinburgh University Medical School, Teviot Place, Edinburgh EH8 9AG, UK.. H.Monaghan@srv4med.ed.ac.uk
SOURCE: HISTOPATHOLOGY, (2001 Dec) 39 (6) 611-9. Journal code: 7704136. ISSN: 0309-0167.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020321
Last Updated on STN: 20020420
Entered Medline: 20020419
AB AIMS: Members of the cadherin and catenin families are involved in chondrogenesis and catenin gene mutations have been detected in malignant tumours of bone. This study was undertaken to assess in detail expression of cadherin, ***beta*** - ***catenin*** and the associated tumour suppressor gene product ***APC*** in bone and cartilage at different stages of human skeletal maturity and in non-neoplastic and neoplastic osteoarticular ***disease*** . METHODS AND RESULTS: Immunohistochemical staining of formalin-fixed paraffin-embedded normal and osteoarthritic adult articular cartilage, fetal growth plate and a series of tumours of bone and cartilage was undertaken with a panel of antibodies against ***APC*** , ***beta*** - ***catenin*** , and pan-cadherin. This study demonstrated expression of ***APC*** , ***beta*** - ***catenin*** and cadherin in normal and diseased bone and cartilage. ***APC*** was present both in osteoblasts and osteoclasts but not in osteocytes. Although only weak ***APC*** staining of occasional growth plate hypertrophic chondrocytes and normal articular chondrocytes was seen, ***APC*** staining was increased in osteoarthritic articular cartilage. ***beta*** - ***catenin*** and pan-cadherin staining was strongly positive in osteoclasts and osteoblasts, with expression being lost when bone cells differentiated into osteocytes. Expression of ***APC*** , ***beta*** - ***catenin*** and pan-cadherin in bone tumours was similar to that of non-neoplastic adult tissues. CONCLUSIONS:

These findings suggest previously unrecognized roles for ***APC*** in regulation of function of chondrocytes, osteoblasts and osteoclasts and support the view that catenin-cadherin ***interactions*** are important in regulation of bone cell activity. Abnormalities of expression or function of these molecules may be important in formation of bone tumours and their clinical behaviour.

L16 ANSWER 7 OF 23 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001241411 MEDLINE
DOCUMENT NUMBER: 21241780 PubMed ID: 11345525
TITLE: A possible role for the WNT-1 pathway in oral carcinogenesis.
AUTHOR: Lo Muzio L
CORPORATE SOURCE: Institute of Dental Sciences, University of Ancona, Italy.. llomuzio@tin.it
SOURCE: CRITICAL REVIEWS IN ORAL BIOLOGY AND MEDICINE, (2001) 12 (2) 152-65. Ref: 231
Journal code: 9009999. ISSN: 1045-4411.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20010917
Entered Medline: 20010913

AB Reductions in cell-cell adhesion and stromal and vascular invasion are essential steps in the progression from localized malignancy to metastatic ***disease*** for all cancers. Proteins involved in intercellular adhesion, such as ***E*** - ***cadherin*** and catenin, probably play an important role in metastatic processes and cellular differentiation. While ***E*** - ***cadherin*** and ***beta*** - ***catenin*** expression has been extensively studied in many forms of human cancers, less is known about the role of the Wingless-Type-1 (WNT-1) pathway in human tumors. A large body of genetic and biochemical evidence has identified ***beta*** - ***catenin*** as a key downstream component of the WNT signaling pathway, and recent studies of colorectal tumors have shown a functional link among ***beta*** - ***catenin*** , adenomatous polyposis coli gene product (***APC***), and other components of the WNT-1 pathway. WNT-1 pathway signaling is thought to be mediated via ***interactions*** between ***beta*** - ***catenin*** and members of the ***LEF*** - ***1*** /TCF family of transcription factors. The WNT signal stabilizes ***beta*** - ***catenin*** protein and promotes its accumulation in the cytoplasm and nucleus. In the nucleus, ***beta*** - ***catenin*** associates with TCF to form a functional transcription factor which mediates the transactivation of target genes involved in the promotion of tumor progression, invasion, and metastasis, such as C-Myc, cyclin D1, c-jun, fra-1, and u-PAR. There is a strong correlation between the ability of the WNT-1 gene to induce ***beta*** - ***catenin*** accumulation and its transforming potential in vivo, suggesting that the WNT-1 gene activates an intracellular signaling pathway that can induce the morphological transformation of cells. For these reasons, data obtained from the study of the WNT-1 pathway could be important in our understanding of the mechanisms of epithelial tumors, in general, and probably also of oral squamous cell carcinoma, in particular.

L16 ANSWER 8 OF 23 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001021408 MEDLINE
DOCUMENT NUMBER: 20449076 PubMed ID: 10896674
TITLE: PAPIN. A novel multiple PSD-95/Dlg-A/ZO-1 protein interacting with neural plakophilin-related armadillo repeat protein/delta-catenin and p0071.
AUTHOR: Deguchi M; Iizuka T; Hata Y; Nishimura W; Hirao K; Yao I; Kawabe H; Takai Y
CORPORATE SOURCE: Takai Biotimer Project, Exploratory Research for Advanced Technology, Japan Science and Technology Corporation, c/o JCR Pharmaceuticals Co. Ltd., Kobe 651-2241, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Sep 22) 275 (38) 29875-80.

Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001103

AB A neural plakophilin-related armadillo repeat protein (NPRAP)/delta-catenin ***interacts*** with one of Alzheimer ***disease*** -related gene products, presenilin 1. We have previously reported the ***interaction*** of NPRAP/delta-catenin with synaptic scaffolding molecule, which is involved in the assembly of synaptic components. NPRAP/delta-catenin also ***interacts*** with ***E*** - ***cadherin*** and ***beta*** - ***catenin*** and is implicated in the organization of cell-cell junctions. p0071, a ubiquitous isoform of NPRAP/delta-catenin, is localized at desmosomes in HeLa and A431 cells and at adherens junctions in Madin-Darby bovine kidney cells. We have identified here a novel protein ***interacting*** with NPRAP/delta-catenin and p0071 and named this protein plakophilin-related armadillo repeat protein- ***interacting*** PSD-95/Dlg-A/ZO-1 (PDZ) protein (PAPIN). PAPIN has six PDZ domains and binds to NPRAP/delta-catenin and p0071 via the second PDZ domain. PAPIN and p0071 are ubiquitously expressed in various tissues and are localized at cell-cell junctions in normal rat kidney cells and bronchial epithelial cells. PAPIN may be a scaffolding protein connecting components of epithelial junctions with p0071.

L16 ANSWER 9 OF 23 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000475436 MEDLINE
DOCUMENT NUMBER: 20437674 PubMed ID: 10980127
TITLE: Beta-catenin, an inducer of uncontrolled cell proliferation and migration in malignancies, is localized in the cytoplasm of vascular endothelium during neovascularization after myocardial infarction.
AUTHOR: Blankesteijn W M; van Gijn M E; Essers-Janssen Y P; Daemen M J; Smits J F
CORPORATE SOURCE: Department of Pharmacology, Cardiovascular Research Institute Maastricht, Universiteit Maastricht, Maastricht, The Netherlands.. wm.blankesteijn@farmaco.unimaas.nl
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (2000 Sep) 157 (3) 877-83. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20000929

AB ***Beta*** - ***catenin*** is a protein involved in cell-cell adhesion and proliferation. In neoplastic ***diseases*** , defects in the regulation of the cellular ***beta*** - ***catenin*** content and cytoplasmic accumulation of the protein contribute to the uncontrolled cell proliferation and migration. Whether ***beta*** - ***catenin*** plays a role in the controlled proliferative and migratory responses to injury, eg, of vascular endothelial cells during neovascularization after myocardial infarction (MI), is not known. In the present study, we examined the localization of ***beta*** - ***catenin*** in the infarcted rat heart at different time points after MI. Cytoplasmic ***beta*** - ***catenin*** was observed in the endothelial cells of the newly formed and pre-existing blood vessels in the infarct area in the first week after MI, but not in the uninjured parts of the heart and not at later time points. Adenomatous polyposis coli (***APC***) protein was also detected; ***interaction*** of ***APC*** with ***beta*** - ***catenin*** has been reported to be critical in epithelial tube formation in vitro. Moreover, the expression of dishevelled-1, an upstream regulatory molecule of the cellular ***beta*** - ***catenin*** content, was observed in vascular endothelial cells in the infarct area. These findings suggest a role for the ***beta*** - ***catenin*** - ***APC*** complex in the

proliferation and migration of vascular endothelial cells during neovascularization of the infarct area.

L16 ANSWER 10 OF 23 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2001105674 MEDLINE
DOCUMENT NUMBER: 20553865 PubMed ID: 11099951
TITLE: The adenomatous polyposis coli (APC) tumour suppressor--genetics, function and disease.
COMMENT: Erratum in: Mol Med Today 2001 Jan;7(1):40
AUTHOR: Sieber O M; Tomlinson I P; Lamlum H
CORPORATE SOURCE: Molecular and Population Genetics Laboratory, Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London, UK, WC2A 3PX.
SOURCE: MOLECULAR MEDICINE TODAY, (2000 Dec) 6 (12) 462-9. Ref: 83
Journal code: 9508560. ISSN: 1357-4310.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010828
Entered Medline: 20010208

AB Mutations in the adenomatous polyposis coli (***APC***) gene are the basis of familial adenomatous polyposis and the majority of sporadic colorectal cancer. ***APC*** is expressed in a wide variety of tissues, ***interacts*** with the cytoskeleton, is involved in regulating levels of ***beta*** - ***catenin*** and, most recently, has been shown to bind DNA, suggesting that it may possess a nuclear role. The mutation spectrum implicated in tumorigenesis and its correlation with ***disease*** phenotype is well characterized and has contributed to our understanding of important functional domains in ***APC*** . Despite these advances, ***APC*** continues to provide a fertile subject of research for both colorectal tumorigenesis and cancer in general.

L16 ANSWER 11 OF 23 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2001078732 MEDLINE
DOCUMENT NUMBER: 20541631 PubMed ID: 11087679
TITLE: Purification of GSK-3 by affinity chromatography on immobilized axin.
AUTHOR: Primot A; Baratte B; Gompel M; Borgne A; Liabeuf S; Romette J L; Jho E H; Costantini F; Meijer L
CORPORATE SOURCE: Station Biologique, CNRS, BP 74, 29682 Roscoff cedex, Bretagne, France.
SOURCE: PROTEIN EXPRESSION AND PURIFICATION, (2000 Dec) 20 (3) 394-404.
Journal code: 9101496. ISSN: 1046-5928.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

AB Glycogen synthase kinase 3 (GSK-3), an element of the Wnt signalling pathway, plays a key role in numerous cellular processes including cell proliferation, embryonic development, and neuronal functions. It is directly involved in ***diseases*** such as cancer (by controlling apoptosis and the levels of ***beta*** - ***catenin*** and cyclin D1), Alzheimer's ***disease*** (tau hyperphosphorylation), and diabetes (as a downstream element of insulin action, GSK-3 regulates glycogen and lipid synthesis). We describe here a rapid and efficient method for the purification of GSK-3 by affinity chromatography on an immobilized fragment of axin. Axin is a docking protein which ***interacts*** with GSK-3ss, ***beta*** - ***catenin*** , phosphatase 2A, and ***APC*** . A polyhistidine-tagged axin peptide (residues 419-672) was produced in Escherichia coli and either immobilized on Ni-NTA agarose beads or purified and immobilized on CNBr-activated Sepharose 4B. These "Axin-His6" matrices were found to selectively bind

recombinant rat GSK-3 beta and native GSK-3 from yeast, sea urchin embryos, and porcine brain. The affinity-purified enzymes displayed high kinase activity. This single step purification method provides a convenient tool to follow the status of GSK-3 (protein level, phosphorylation state, kinase activity) under various physiological settings. It also provides a simple and efficient way to purify large amounts of active recombinant or native GSK-3 for screening purposes. Copyright 2000 Academic Press.

L16 ANSWER 12 OF 23 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2001065715 MEDLINE
DOCUMENT NUMBER: 20556428 PubMed ID: 11102958
TITLE: Detection and analysis of beta-catenin mutations in prostate cancer.
AUTHOR: Chesire D R; Ewing C M; Sauvageot J; Bova G S; Isaacs W B
CORPORATE SOURCE: Brady Urological Institute, Research Laboratories, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21287, USA.
CONTRACT NUMBER: CA-15416 (NCI)
CA-58236 (NCI)
SOURCE: PROSTATE, (2000 Dec 1) 45 (4) 323-34.
Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222
AB BACKGROUND: ***E*** - ***cadherin*** and alpha-catenin are components of adherens junctions which mediate calcium-dependent, cell-cell adhesion in a homotypic manner. Both these molecules have been defined as useful tumor markers as their altered expression correlates with increased tumor aggressiveness and dedifferentiation. More recently, alterations of a third component of adherens junctions, ***beta*** - ***catenin*** , have been observed to play a role in several human cancers. Dysregulation of ***beta*** - ***catenin*** , either by direct mutation or by defects in ***interacting*** pathways/regulators, can result in its cytoplasmic accumulation and nuclear translocation. In the nucleus, ***beta*** - ***catenin*** forms a transcriptional complex capable of upregulating target genes, many of which encode proliferative factors. Given its oncogenic activity and connection to human cancer, we examined the ***beta*** - ***catenin*** gene and its expression in prostate cancer. METHODS: By single-stranded conformational polymorphism (SSCP) and DNA sequencing analyses, we screened exon 3 of ***beta*** - ***catenin*** from a panel of 81 primary tumors obtained at radical prostatectomy, 22 lymph node metastases from untreated patients, and a unique set of 61 metastatic tissues from 19 patients who died of hormone-refractory ***disease*** . RESULTS: We found putative activating mutations (missense and deletion) at a rate of 5% (7/138). One patient had the same 72 base pair deletion in each of nine separate metastases examined, indicating that this change was associated with a clonal population of metastatic cells. CONCLUSIONS: Immunohistological staining of mutation-positive tumors demonstrated ***beta*** - ***catenin*** accumulation and nuclear localization in a heterogeneous fashion. Consistent with this in vivo finding, our in vitro analyses demonstrate that certain mutations can result in increased ***beta*** - ***catenin*** nuclear activity in prostate cancer cell lines. These data implicate the ***beta*** - ***catenin*** signaling pathway in the development of a subset of prostate cancers. Copyright 2000 Wiley-Liss, Inc.

L16 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:97123 BIOSIS
DOCUMENT NUMBER: PREV200100097123
TITLE: Function and molecular organization of the presenilin1/E-cadherin/catenin adherens junction system.
AUTHOR(S): Marambaud, P. (1); Baki, L.; Georgakopoulos, A.; Shioi, J.; Efthimiopoulos, S.; Ozawa, M.; Robakis, N. K.
CORPORATE SOURCE: (1) Mount Sinai School of Medicine, New York, NY USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No.

1-2, pp. Abstract No.-298.13. print.
Meeting Info. [redacted]th Annual Meeting of the Soci[redacted] of Neuroscience New Orleans, LA, USA November 04-09, 2000
Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Most cases of early onset familial Alzheimer's ***disease*** (FAD) are caused by mutations in presenilin 1 gene. We found that in epithelial cells, presenilin 1 (PS1) protein localizes at cell-cell contact sites and forms complexes with the cadherin-based adherens junctions. The cytoplasmic domain of cell surface cadherin regulates cell-cell adhesion by ***interacting*** with soluble protein factors, including beta- and gamma-catenin. We used ***E*** - ***cadherin*** deletion mutants which lack the beta-, and gamma-catenin binding sequence to show that the PS1/ ***E*** - ***cadherin*** ***interaction*** is independent of the catenin binding. Cross-linking experiments revealed that the cleaved carboxy-terminal fragment of PS1 binds directly to ***E*** - ***cadherin*** and an 11 amino acid sequence in the cytoplasmic domain of ***E*** - ***cadherin*** is necessary for this ***interaction*** . Furhtermore, absence of PS1 destabilizes both the ***E*** - ***cadherin*** / ***beta*** - ***catenin*** and ***E*** - ***cadherin*** /gamma-catenin complexes. Thus, our data shows that PS1 binds directly to the cytoplasmic domain of ***E*** - ***cadherin*** and stabilizes the cadherin/catenin cell-cell adhesion complex. Adherens junctions regulate cell-cell adhesion/communication and play important roles not only in organogenesis but also in tissue function of adult organisms. Incorporation of mutated PS1 in adherens junctions may affect function of many tissues including synaptic adhesion and permeability of the brain endothelium (supported by HIH grant AG08200, the Alzheimer Association and the Philippe Foundation).

L16 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:549289 CAPLUS
DOCUMENT NUMBER: 131:194280
TITLE: Agents for treating cancer and other human illnesses based on .beta.-catenin
INVENTOR(S): Birchmeier, Walter; Von Kries, Jens-Peter
PATENT ASSIGNEE(S): Max-Delbrueck-Centrum fuer Molekulare Medizin, Germany
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942481	A2	19990826	WO 1999-DE554	19990222
WO 9942481	A3	20000210		
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19909251	A1	19990826	DE 1999-19909251	19990222
EP 1054899	A2	20001129	EP 1999-913097	19990222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
JP 2002505255	T2	20020219	JP 2000-532433	19990222

PRIORITY APPLN. INFO.: DE 1998-19807390 A 19980221
WO 1999-DE554 W 19990222

AB C.beta.-catenin is a central mol. of the Wnt signal path. Increasing .beta.-catenin in the cell leads to its translocation into the cell nucleus and to its interaction with transcription factors of the LEF-1/TCF family. This can lead to colonic cancers and melanomas (oncogenic signal path). However, .beta.-catenin also interacts with the tumor-suppressor genes APC, conductin, and E-cadherin, which have a contrary effect on the cell (antioncogenic effect). Peptides derived from LEF-1-/TCF-4 transcription factors and analogous mols. can be used in the treatment of tumors, esp. colonic cancers and melanomas. These peptides and analogous mols. influence the interaction between .beta.-catenin and LEF-1/TCF. The peptides comprise parts of the LEF-1/TCF-4 transcription factors and variants and mutations thereof, preferably the 10-40 N-terminal amino

acids of LEF-1 or TCF-4, as well as peptides derived from the armadillo region of .beta.-catenin which were identified as interaction domains with LEF-1/TCF, APC, conductin, and E-cadherin. The peptides constituting interaction domains with APC or conductin can increase the concn. of .beta.-catenin in the cell. These last mols. can be used to influence the formation of tissues and organs, e.g. to promote hair growth.

L16 ANSWER 15 OF 23 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999194751 MEDLINE
DOCUMENT NUMBER: 99194751 PubMed ID: 10092585
TITLE: Direct interaction of Alzheimer's disease-related presenilin 1 with armadillo protein p0071.
AUTHOR: Stahl B; Diehlmann A; Sudhof T C
CORPORATE SOURCE: Max Planck Institute for Experimental Medicine, 37075 Gottingen, Germany.. stahl@mail.mpiem.gwdg.de
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Apr 2) 274 (14) 9141-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990427
AB Alzheimer's ***disease*** -related presenilins are thought to be involved in Notch signaling during embryonic development and/or cellular differentiation. Proteins mediating the cellular functions of the presenilins are still unknown. We utilized the yeast two-hybrid system to identify an ***interacting*** armadillo protein, termed p0071, that binds specifically to the hydrophilic loop of presenilin 1. In vivo, the presenilins constitutively undergo proteolytic processing, forming two stable fragments. Here, we show that the C-terminal fragment of presenilin 1 directly binds to p0071. Nine out of 10 armadillo repeats in p0071 are essential for mediating this ***interaction*** . Since armadillo proteins, like ***beta*** - ***catenin*** and ***APC*** , are known to participate in cellular signaling, p0071 may function as a mediator of presenilin 1 in signaling events.

L16 ANSWER 16 OF 23 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1999274728 MEDLINE
DOCUMENT NUMBER: 99274728 PubMed ID: 10341227
TITLE: Presenilin 1 facilitates the constitutive turnover of beta-catenin: differential activity of Alzheimer's disease-linked PS1 mutants in the beta-catenin-signaling pathway.
AUTHOR: Kang D E; Soriano S; Frosch M P; Collins T; Naruse S; Sisodia S S; Leibowitz G; Levine F; Koo E H
CORPORATE SOURCE: Department of Neurosciences, University of California, San Diego, La Jolla, California 92093, USA.
CONTRACT NUMBER: NS28121 (NINDS)
SOURCE: JOURNAL OF NEUROSCIENCE, (1999 Jun 1) 19 (11) 4229-37.
Journal code: 8102140. ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 20010521
Entered Medline: 19990616
AB Although an association between the product of the familial Alzheimer's ***disease*** (FAD) gene, presenilin 1 (PS1), and ***beta*** - ***catenin*** has been reported recently, the cellular consequences of this ***interaction*** are unknown. Here, we show that both the full length and the C-terminal fragment of wild-type or FAD mutant PS1 ***interact*** with ***beta*** - ***catenin*** from transfected cells and brains of transgenic mice, whereas ***E*** - ***cadherin*** and adenomatous polyposis coli (***APC***) are not detected in this complex. Inducible overexpression of PS1 led to increased association of ***beta*** - ***catenin*** with glycogen synthase kinase-3beta

(GSK-3beta), a negative regulator of ***beta*** - ***catenin*** , and accelerated the turnover of endogenous ***beta*** - ***catenin*** . In support of this finding, the ***beta*** - ***catenin*** half-life was dramatically longer in fibroblasts deficient in PS1, and this phenotype was completely rescued by replacement of PS1, demonstrating that PS1 normally stimulates the degradation of ***beta*** - ***catenin*** . In contrast, overexpression of FAD-linked PS1 mutants (M146L and DeltaX9) failed to enhance the association between GSK-3beta and ***beta*** - ***catenin*** and interfered with the constitutive turnover of ***beta*** - ***catenin*** . In vivo confirmation was demonstrated in the brains of transgenic mice in which the expression of the M146L mutant PS1 was correlated with increased steady-state levels of endogenous ***beta*** - ***catenin*** . Thus, our results indicate that PS1 normally promotes the turnover of ***beta*** - ***catenin*** , whereas PS1 mutants partially interfere with this process, possibly by failing to recruit GSK-3beta into the PS1- ***beta*** - ***catenin*** complex. These findings raise the intriguing possibility that PS1- ***beta*** - ***catenin*** ***interactions*** and subsequent activities may be consequential for the pathogenesis of AD.

L16 ANSWER 17 OF 23 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1999285630 MEDLINE
DOCUMENT NUMBER: 99285630 PubMed ID: 10359135
TITLE: Intracellular distribution of beta-catenin in colorectal adenomas, carcinomas and Peutz-Jeghers polyps.
AUTHOR: Herter P; Kuhnen C; Muller K M; Wittinghofer A; Muller O
CORPORATE SOURCE: Max-Planck-Institut fur Molekulare Physiologie, Dortmund, Germany.. peter.herter@mpi-dortmund.mpg.de
SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1999) 125 (5) 297-304.
Journal code: 7902060. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990615

AB The ***interaction*** of the adenomatous polyposis coli (***APC***) tumor-suppressor protein and the intracellular cell-adhesion protein ***beta*** - ***catenin*** is crucial for the development of colorectal tumors. Since functional nuclear complexes of ***beta*** - ***catenin*** with transcription factors have been identified recently, the knowledge of level and distribution of ***beta*** - ***catenin*** in sporadic colorectal tumors will give important insights into the intracellular mechanism of sporadic colorectal tumor initiation and progression. In contrast to the familiar adenomatous polyposis syndrome and to the majority of sporadic colorectal tumors, Peutz-Jeghers (PJ) syndrome is not caused by mutations in the ***APC*** gene. Since PJ syndrome is an inherited ***disease*** with an increased risk for gastrointestinal adenocarcinoma, whether ***beta*** - ***catenin*** plays a similarly important role for the development of PJ polyps should be further investigated. For these reasons we analyzed the distribution of ***beta*** - ***catenin*** in a total of 60 sporadic colorectal tumors at different stages of progression and in 6 PJ polyps. In addition to the localization at the cell-to-cell border membranes, fluorescence immunohistochemistry revealed a nuclear accumulation of ***beta*** - ***catenin*** in single tumor cells of 10/14 small adenomas with mild dysplasia and in 14/16 adenomas with moderate dysplasia. Further tumor progression is accompanied by an expansion of cells with increased level of nuclear and cytoplasmic ***beta*** - ***catenin*** . These cells were observed in 5/16 adenomas with moderate dysplasia and in 15/15 adenomas with severe dysplasia. In all adenocarcinomas investigated, as well as in the corresponding lymph node metastases, a sub-population of tumor cells exhibited a remarkably increased level of ***beta*** - ***catenin*** within the entire cytoplasm and the nucleus. In contrast to the situation in sporadic colorectal tumors, nuclear and cytoplasmic ***beta*** - ***catenin*** was not increased in PJ polyps. These results point to an extensive redistribution of ***beta*** - ***catenin*** , which starts early in colorectal tumorigenesis. The nuclear accumulation in single cells of small adenomas can be considered

as the first visible sign of the loss of ***APC*** function. Thus the immunohistochemical detection of ***beta*** - ***catenin*** distribution could serve as a criterion for estimating the malignant potential in the clinico-pathological evaluation of colon tumors during their early progression.

L16 ANSWER 18 OF 23 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 1999137657 MEDLINE
DOCUMENT NUMBER: 99137657 PubMed ID: 9950951
TITLE: Nuclear localization of beta-catenin and loss of apical brush border actin in cystic tubules of bcl-2 -/- mice.
AUTHOR: Sorenson C M
CORPORATE SOURCE: George M. O'Brien Kidney and Urological Diseases Center, Renal Division, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, 63110, USA.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 Feb) 276 (2 Pt 2) F210-7.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990413
Last Updated on STN: 19990413
Entered Medline: 19990330
AB Tight regulation of the rates of cell proliferation and apoptosis is critical for normal nephrogenesis. Nephrogenesis is profoundly affected by the loss of bcl-2 expression. Bcl-2-deficient (bcl-2 -/-) mice are born with renal hypoplasia and succumb to renal failure secondary to renal multicystic ***disease*** . Cell-cell and cell-matrix ***interactions*** impact tissue architecture by modulating cell proliferation, migration, differentiation, and apoptosis. ***E*** - ***cadherin*** mediates calcium-dependent homotypic cell-cell ***interactions*** that are stabilized by its association with catenins and the actin cytoskeleton. The contribution of altered cell-cell ***interactions*** to renal cystic ***disease*** has not been delineated. Cystic kidneys from bcl-2 -/- mice displayed nuclear localization of ***beta*** - ***catenin*** and loss of apical brush border actin staining. The protein levels of alpha-catenin, ***beta*** - ***catenin*** , actin, and ***E*** - ***cadherin*** were not altered in cystic kidneys compared with normal kidneys. Therefore, an altered distribution of ***beta*** - ***catenin*** and actin, in kidneys from bcl-2 -/- mice, may indicate improper cell-cell ***interactions*** interfering with renal maturation and contributing to renal cyst formation.

L16 ANSWER 19 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:135249 SCISEARCH
THE GENUINE ARTICLE: 164RR
TITLE: Nuclear localization of beta-catenin and loss of apical brush border actin in cystic tubules of bcl-2 -/- mice
AUTHOR: Sorenson C M (Reprint)
CORPORATE SOURCE: WASHINGTON UNIV, SCH MED, DIV RENAL, GEORGE M OBRIEN KIDNEY & UROL DIS CTR, DEPT MED, BOX 8126, ST LOUIS, MO 63110 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-RENAL PHYSIOLOGY, (FEB 1999)
Vol. 45, No. 2, pp. F210-F217.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0363-6127.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 23
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Tight regulation of the rates of cell, proliferation and apoptosis is critical for normal nephrogenesis. Nephrogenesis is profoundly affected by the loss of bcl-2 expression. Bcl-2-deficient (bcl-2 -/-) mice are born with renal hypoplasia and succumb to renal failure secondary to renal

multicystic ***disease*** . Cell-cell and cell-matrix ***interactions*** impact tissue architecture by modulating cell proliferation, migration, differentiation, and apoptosis. ***E*** - ***cadherin*** mediates calcium-dependent homotypic cell-cell ***interactions*** that are stabilized by its association with catenins and the actin cytoskeleton. The contribution of altered cell-cell ***interactions*** to renal cystic ***disease*** has not been delineated. Cystic kidneys from bcl-2 -/- mice displayed nuclear localization of ***beta*** - ***catenin*** and loss of apical brush border actin staining. The protein levels of alpha-catenin, ***beta*** - ***catenin*** , actin, and ***E*** - ***cadherin*** were not altered in cystic kidneys compared with normal kidneys. Therefore, an altered distribution of ***beta*** - ***catenin*** and actin, in kidneys from bcl-2 -/- mice, may indicate improper cell-cell ***interactions*** interfering with renal maturation and contributing to renal cyst formation.

L16 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:672440 CAPLUS
DOCUMENT NUMBER: 129:272659
TITLE: Compositions and methods for diagnosing/treating disease based on .beta.-catenin/transcription factor interactions
INVENTOR(S): Polakis, Paul; Rubinfeld, Bonnee
PATENT ASSIGNEE(S): Onyx Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9842296	A2	19981001	WO 1998-US5416	19980318
WO 9842296	A3	19990325		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9868661	A1	19981020	AU 1998-68661	19980318
EP 970120	A2	20000112	EP 1998-914260	19980318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002504808	T2	20020212	JP 1998-545805	19980318

PRIORITY APPLN. INFO.: US 1997-41685P P 19970324
WO 1998-US5416 W 19980318

AB Methods and compns. are described that are useful for diagnosing and/or treating disease arising from unwanted cell growth, preferably cancer, involving diagnosing cells for stabilized .beta.-catenin, or treating cells with compds. that disrupt or alter the formation of a complex consisting of .beta.-catenin/transcription factor, where the transcription factor is a member of the Lef/Tcf family. .beta.-Catenin and APC protein were analyzed in melanoma cell lines. Of the 26 melanoma cell lines examd., 8 are defective in .beta.-catenin regulation because of .beta.-catenin mutations, unusual .beta.-catenin mRNA splicing, or inactivation of APC. Transcription factor LEF1 was preferentially coimmunopptd. by anti-.beta.-catenin from melanoma cells contg. stabilized .beta.-catenin.

L16 ANSWER 21 OF 23 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 1998429380 MEDLINE
DOCUMENT NUMBER: 98429380 PubMed ID: 9758413
TITLE: Expression of the anhidrotic ectodermal dysplasia gene is reduced in skin cancer coinciding with reduced E-cadherin.
AUTHOR: Montonen O; Ezer S; Laurikkala J; Karjalainen-Lindsberg M L; Thesleff I; Kere J; Saarialho-Kere U
CORPORATE SOURCE: Department of Medical Genetics, Haartman Institute,

University of Helsinki, and Helsinki University Central Hospital, Finl[redacted].
SOURCE: EXPERIMENTAL DERMATOLOGY, (1998 Aug) 7 (4) 168-74.
Journal code: 9301549. ISSN: 0906-6705.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981223

AB X-linked anhidrotic ectodermal dysplasia (EDA) is characterized by defects in the development of hair, teeth, and sweat glands. We have recently cloned the gene for EDA by positional cloning. The EDA gene encodes a transmembrane protein with a putative role in epithelial mesenchymal ***interactions*** . Since EDA could play a role in cell-cell or cell-matrix adhesion, acantholytic skin ***diseases*** and several types of non-invasive and invasive skin cancers were studied using in situ hybridization. Because of the observation that the promoter region of the EDA gene contains a binding site for ***LEF*** - ***1*** , which is involved in the signaling through ***E*** - ***cadherin*** / ***beta*** ***catenin*** complex, we compared the expression of EDA with immunolocalization for ***E*** - ***cadherin*** (E-CD). EDA expression during hair growth cycle, in benign adnexal tumors, and neuroectoderm-derived nevus cells was also examined. Our findings indicate that EDA expression is less abundant in malignant tumors, including basal and squamous cell carcinomas and melanoma, and in acantholytic keratinocytes compared to normal epidermis. The reduction in expression also coincides with diminished E-CD staining in all malignant cell types and in acantholytic cells. Our results suggest that EDA protein functions in the regulation of epithelial cell contacts and that it may be associated with the E-CD signaling pathway.

L16 ANSWER 22 OF 23 MEDLINE
ACCESSION NUMBER: 97311893 MEDLINE
DOCUMENT NUMBER: 97311893 PubMed ID: 9244653
TITLE: [Molecular etiology of colorectal carcinogenesis, clinical manifestations and therapy].
Molekulare Ursachen kolorektaler Kanzerogenese, klinische Manifestation und Therapie.
AUTHOR: Jacobasch G; Jacobasch K H
CORPORATE SOURCE: Deutsches Institut fur Ernahrungsforschung Potsdam-Rehbrucke und Onkologische Schwerpunktpraxis, Berlin.
SOURCE: ZEITSCHRIFT FUR ARZTLICHE FORTBILDUNG UND QUALITATSSICHERUNG, (1997 Mar) 91 (2) 125-33. Ref: 47
Journal code: 9707934. ISSN: 1431-7621.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970806

AB Mutations of tumor suppressor genes, of the mismatch DNA repair system, and of the TGF-beta-II-receptor are the main causes for a higher risk of colorectal cancer. Among mutations of the Ape gene, which characterize the clinical manifestation of the familial polyposis (FAP), point mutations are dominating which create new stop codons or arise from deletions or insertions of nucleotides causing frame shifts. Because the binding site of ***beta*** - ***catenin*** is localized in the C-terminus of the Ape protein, disturbances result in the cellular signal transfer from its loss. Consequently, the ***interactions*** of the usually formed Ape- ***beta*** - ***catenin*** complex with the cytoskeleton and the cadherin system in the plasma membrane as well as the translocation of ***beta*** - ***catenin*** into the nucleus cannot be realized. Mutations in the genes of the mismatch DNA repair system and of the TGF-beta-II-receptor, the main defects of the HNPCC (hereditary

nonpolyposis colorectal cancer), are exclusively identified in sequences of microsatellites. Because t[redacted]majority of ***Apc*** gene[redacted]tations is also localized in repetitive motifs even in CpG islands primary disturbances are to postulate in the methylation pattern of the genes producing germline and somatic mutations. Generally, complexly connected reactions are involved in this cascade of colorectal cancer genesis. This fact explains the relatively late clinical manifestation of the ***disease*** and offers the possibility to identify carriers with an increased risk of colorectal cancer development in order to integrate them into a programme of control and preventive medicine. Beside the known treatment by surgery and cytostatics, inhibitors of prostaglandin synthesis gain therapeutic significance. Cancerogenesis can be efficiently suppressed by inhibition of the COX-2-induction (cyclo-oxygenase-2). There is a lack of clinical experience for a decision whether a high intraluminal level of butyrate in the large intestine can delay colorectal carcinogenesis.

L16 ANSWER 23 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:94330 BIOSIS
DOCUMENT NUMBER: PREV199799393533
TITLE: Interaction of the APC tumor suppressor protein with catenins.
AUTHOR(S): Rubinfeld, Bonnee; Albert, Iris; Porfiri, Emilio; Munemitsu, Susan; Polakis, Paul
CORPORATE SOURCE: Onyx Pharmaceuticals, 3031 Research Drive, Richmond, CA 94806 USA
SOURCE: Molecular Biology of the Cell, (1996) Vol. 7, No. SUPPL., pp. 4A.
Meeting Info.: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996
ISSN: 1059-1524.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 14:52:14 ON 28 JUL 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 14:53:00 ON 28 JUL 2002
L1 13144 S BETA-CATENIN
L2 55071 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L3 5750 S L1 (P) L2
L4 1449 S L3 (P) INTERACT?
L5 16 S L4 (P) (PEPTIDE OR AGENT) (P) (IINHIBIT? OR PROMOT? OR AFFEC
L6 40 S L4 (P) (PEPTIDE OR AGENT) (P) (INHIBIT? OR PROMOT? OR AFFECT
L7 11 DUPLICATE REMOVE L6 (29 DUPLICATES REMOVED)
L8 84 S (HIS 470) OR (ARG 469) OR (TRP 383) OR (ARG 386) OR (PHE 253)
L9 0 S L8 (P) L1
L10 3359 S L1 (P) MUTAT?
L11 123 S (HIS470) OR (ARG469) OR (TRP383) OR (ARG386) OR (PHE253) OR (
L12 0 S L1 (P) L11
L13 1859 S L10 (P) L2
L14 1449 S L3 (P) INTERACT?
L15 66 S L14 (P) (DISEASE OR ILLNESS)
L16 23 DUPLICATE REMOVE L15 (43 DUPLICATES REMOVED)

=> s l1 (p) (armadillo domain)
L17 17 L1 (P) (ARMADILLO DOMAIN)

=> s l17 (p) l2
L18 5 L17 (P) L2

=> duplicate remove l18
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L18
L19 2 DUPLICATE REMOVE L18 (3 DUPLICATES REMOVED)

=> d l19 1-2 ibib abs

L19 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:208094 CAPLUS
DOCUMENT NUMBER: 134:247261
TITLE: Agents for treating human diseases, especially for treating tumors such as colon cancers and melanomas or for regenerating tissue and promoting hair growth
INVENTOR(S): Birchmeier, Walter; Von Kries, Jens-peter
PATENT ASSIGNEE(S): Max-Delbruck-Centrum fur Molekulare Medizin, Germany
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019353	A2	20010322	WO 2000-DE3104	20000907
WO 2001019353	A3	20020328		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19944404	A1	20010322	DE 1999-19944404	19990916
EP 1214345	A2	20020619	EP 2000-972578	20000907
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: DE 1999-19944404 A 19990916
WO 2000-DE3104 W 20000907

AB The invention relates to agents for treating human diseases which are based on substances that specifically influence the binding of .beta.-catenin with LEF-1/TCF transcription factors, APC or conductin/axin. The invention particularly relates to the identification and use of hydrophobic pockets on the mol. surface in the proximity of the essential binding points for the binding partners of .beta.-catenin with the aim of optimizing these substances. The invention also relates to the use of the substances, preferably for treating tumors, e.g. colon cancers and melanomas, or for regenerating tissue and promoting hair growth.

L19 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001342194 MEDLINE
DOCUMENT NUMBER: 21282973 PubMed ID: 11279024
TITLE: Regulation of beta-catenin structure and activity by tyrosine phosphorylation.
AUTHOR: Piedra J; Martinez D; Castano J; Miravet S; Dunach M; de Herreros A G
CORPORATE SOURCE: Unitat de Biologia Cel.lular i Molecular, Institut Municipal d'Investigacio Medica, Universitat Pompeu Fabra, c/Dr. Aiguader 80, 08003 Barcelona, Spain.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 8) 276 (23) 20436-43.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712

AB ***beta*** - ***Catenin*** plays a dual role as a key effector in the regulation of adherens junctions and as a transcriptional coactivator. Phosphorylation of Tyr-654, a residue placed in the last armadillo repeat of ***beta*** - ***catenin*** , decreases its binding to ***E*** - ***cadherin*** . We show here that phosphorylation of Tyr-654 also

stimulates the association of ***beta*** - ***catenin*** to the basal transcription factor TA[redacted]binding protein. The structura[redacted]ases of these different affinities were investigated. Our results indicate that the ***beta*** - ***catenin*** C-terminal tail interacts with the armadillo repeat domain, hindering the association of the armadillo region to the TATA-binding protein or to ***E*** - ***cadherin*** . Phosphorylation of ***beta*** - ***catenin*** Tyr-654 decreases armadillo-C-terminal tail association, uncovering the last armadillo repeats. In a C-terminal-depleted ***beta*** - ***catenin*** , the presence of a negative charge at Tyr-654 does not affect the interaction of the TATA-binding protein to the ***armadillo*** ***domain*** . However, in the case of ***E*** - ***cadherin*** , the establishment of ion pairs dominates its association with ***beta*** - ***catenin*** , and its binding is greatly dependent on the absence of a negative charge at Tyr-654. Thus, phosphorylation of Tyr-654 blocks the Ecadherin-***beta*** - ***catenin*** interaction, even though the steric hindrance of the C-tail is no longer present. These results explain how phosphorylation of ***beta*** - ***catenin*** in Tyr-654 modifies the tertiary structure of this protein and the interaction with its different partners.

```
=> d his

     (FILE 'HOME' ENTERED AT 14:52:14 ON 28 JUL 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     14:53:00 ON 28 JUL 2002
L1         13144 S BETA-CATENIN
L2         55071 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L3          5750 S L1 (P) L2
L4          1449 S L3 (P) INTERACT?
L5            16 S L4 (P) (PEPTIDE OR AGENT) (P) (IINHIBIT? OR PROMOT? OR AFFEC
L6            40 S L4 (P) (PEPTIDE OR AGENT) (P) (INHIBIT? OR PROMOT? OR AFFECT
L7            11 DUPLICATE REMOVE L6 (29 DUPLICATES REMOVED)
L8            84 S (HIS 470) OR (ARG 469) OR (TRP 383) OR (ARG 386) OR (PHE 253)
L9             0 S L8 (P) L1
L10         3359 S L1 (P) MUTAT?
L11          123 S (HIS470) OR (ARG469) OR (TRP383) OR (ARG386) OR (PHE253) OR (
L12            0 S L1 (P) L11
L13         1859 S L10 (P) L2
L14         1449 S L3 (P) INTERACT?
L15           66 S L14 (P) (DISEASE OR ILLNESS)
L16           23 DUPLICATE REMOVE L15 (43 DUPLICATES REMOVED)
L17           17 S L1 (P) (ARMADILLO DOMAIN)
L18            5 S L17 (P) L2
L19            2 DUPLICATE REMOVE L18 (3 DUPLICATES REMOVED)

=> s l4 (p) (n-terminal) (p) (papteide or fragment)
L20            5 L4 (P) (N-TERMINAL) (P) (PAPTEIDE OR FRAGMENT)

=> duplicate remove l20
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L20
L21            1 DUPLICATE REMOVE L20 (4 DUPLICATES REMOVED)

=> d l21 1 ibib abs

L21  ANSWER 1 OF 1     MEDLINE                              DUPLICATE 1
ACCESSION NUMBER:    2002003046     MEDLINE
DOCUMENT NUMBER:     21623063   PubMed ID: 11751639
TITLE:               Chromatin-specific regulation of LEF-1-beta-catenin
                     transcription activation and inhibition in vitro.
AUTHOR:              Tutter A V; Fryer C J; Jones K A
CORPORATE SOURCE:    Regulatory Biology Laboratory, The Salk Institute for
                     Biological Studies, La Jolla, California 92037, USA.
SOURCE:              GENES AND DEVELOPMENT, (2001 Dec 15) 15 (24) 3342-54.
                     Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
```

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020125
Entered Medline: 20020122

AB Transcriptional activation of Wnt/Wg-responsive genes requires the stabilization and nuclear accumulation of ***beta*** - ***catenin*** , a dedicated coactivator of LEF/TCF enhancer-binding proteins. Here we report that recombinant ***beta*** - ***catenin*** strongly enhances binding and transactivation by ***LEF*** - ***1*** on chromatin templates in vitro. Interestingly, different ***LEF*** - ***1*** isoforms vary in their ability to bind nucleosomal templates in the absence of ***beta*** - ***catenin*** , owing to ***N*** - ***terminal*** residues that repress binding to chromatin, but not nonchromatin, templates. Transcriptional activation in vitro requires both the armadillo (ARM) repeats and the C terminus of ***beta*** - ***catenin*** , whereas the phosphorylated N terminus is inhibitory to transcription. A ***fragment*** spanning the C terminus (CT) and ARM repeats 11 and 12 (CT-ARM), but not the CT alone, functions as a dominant negative inhibitor of ***LEF*** - ***1*** -beta-cat activity in vitro and can block ATP-dependent binding of the complex to chromatin. ***LEF*** - ***1*** -beta-cat transactivation in vitro was also repressed by inhibitor of ***beta*** - ***catenin*** and ***Tcf*** - ***4*** (ICAT), a physiological inhibitor of Wnt/Wg signaling that ***interacts*** with ARM repeats 11 and 12, and by the nonsteroidal anti-inflammatory compound, sulindac. None of these transcription inhibitors (CT-ARM, ICAT, or sulindac) could disrupt the ***LEF*** - ***1*** -beta-cat complex after it was stably bound to chromatin. We conclude that the CT-ARM region of ***beta*** - ***catenin*** functions as a chromatin-specific activation domain, and that several inhibitors of the Wnt/Wg pathway directly modulate ***LEF*** - ***1*** -beta-cat activity on chromatin.

=> d his

(FILE 'HOME' ENTERED AT 14:52:14 ON 28 JUL 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 14:53:00 ON 28 JUL 2002

```
L1        13144 S BETA-CATENIN
L2        55071 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L3         5750 S L1 (P) L2
L4         1449 S L3 (P) INTERACT?
L5           16 S L4 (P) (PEPTIDE OR AGENT) (P) (IINHIBIT? OR PROMOT? OR AFFEC
L6           40 S L4 (P) (PEPTIDE OR AGENT) (P) (INHIBIT? OR PROMOT? OR AFFECT
L7           11 DUPLICATE REMOVE L6 (29 DUPLICATES REMOVED)
L8           84 S (HIS 470) OR (ARG 469) OR (TRP 383) OR (ARG 386) OR (PHE 253)
L9            0 S L8 (P) L1
L10        3359 S L1 (P) MUTAT?
L11         123 S (HIS470) OR (ARG469) OR (TRP383) OR (ARG386) OR (PHE253) OR (
L12           0 S L1 (P) L11
L13        1859 S L10 (P) L2
L14        1449 S L3 (P) INTERACT?
L15          66 S L14 (P) (DISEASE OR ILLNESS)
L16          23 DUPLICATE REMOVE L15 (43 DUPLICATES REMOVED)
L17          17 S L1 (P) (ARMADILLO DOMAIN)
L18           5 S L17 (P) L2
L19           2 DUPLICATE REMOVE L18 (3 DUPLICATES REMOVED)
L20           5 S L4 (P) (N-TERMINAL) (P) (PAPTEIDE OR FRAGMENT)
L21           1 DUPLICATE REMOVE L20 (4 DUPLICATES REMOVED)
```

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	134.43	134.64
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-4.34	-4.34

STN INTERNATIONAL LOGOFF AT 15:06:10 ON 28 JUL 2002